Original Research Article

Association of Serum Uric Acid Levels with Micro Vascular Complications of Diabetes

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) was one of the most challenging health problems and Uric acid levels were positively associated with serum glucose levels in healthy subjects. The aim of the study was to evaluate the association between serum uric acid level in diabetic patients with and without microvascular complications, which include diabetic nephropathy (DN), diabetic retinopathy (DR), and diabetic peripheral neuropathy (PN).

Material and methods: A cross-sectional study was conducted on Patients with known diabetes at NRI Medical College in the department of General Medicine. The study was conducted from January 2018 to June 2018. A total of 80 subjects were included in the study and divided into two groups, 40 with microvascular complications of diabetes and 40 without microvascular complications. A biochemical investigation like fasting and post-prandial blood glucose estimation, urine examination, glycosylated hemoglobin estimation, lipid profile, uric acid was recorded. IBM 22 software was used for statistical analysis.

Results: The mean age was 54.88 ±12.77 among diabetic with microvascular complications, 60.33 ±12.33 among diabetic without microvascular complications. Plasma uric acid was highest among Diabetic with complications (6.61±1.81). Nephropathy patients had lower uric acid (6.3±2.66) than in subjects with retinopathy and neuropathy. Hyperuricemia (28.57%) was reported among patients with more than 10 years duration of diabetes.

Conclusion: Uric acid is useful as predictors for monitoring the chronic microvascular complications in patients with type 2 diabetes.

Key words

Diabetes Miletus, Uric Acid, Nephropathy.

Introduction

Type 2 diabetes mellitus (T2DM) is undoubtedly one of the most challenging health problems in the 21st century and the number of diabetic patients diagnosed by the international diabetes federation in the 8th edition of IDF atlas 2017 estimated the worldwide prevalence to be 425 million in 2017 [1]. Several micros and macrovascular complications of diabetes arise with increasing duration of diabetes. The chronic microvascular complications are a serious problem, which includes diabetic nephropathy (DN), diabetic retinopathy (DR), and diabetic peripheral neuropathy (PN). Complications due to diabetes are a major cause of disability, reduced quality of life and death [2].

Uric acid (UA) is the end product of purine metabolism in humans. Its concentration is determined by the collaboration of genetic and environmental factors. Additionally, SUA could also lead to endothelial dysfunction by inhibiting the bioavailability of nitric oxide (NO), the progression of which might cause vascular lesions and even death [3].

UA levels is positively associated with serum glucose levels in healthy subjects [4]. Studies have established that UA levels are higher in subjects with prediabetes and early Type 2 diabetes than in healthy controls [5, 6] and, two recent meta-analyses revealed that elevated SUA has been an independent risk factor for the development of type 2 diabetes (T2DM) [7]. Recently, it has been found that there is a definitive relation between hyperglycemia and uric acid levels.

Diabetic retinopathy (DR) diabetic nephropathy (DN), Diabetic peripheral neuropathy (DPN) is three of the chronic microvascular complications in type 2 diabetes mellitus (DM). DR is a major cause of vision loss in adults, causing severe morbidity in patients with diabetes, resulting in public health and economic burdens [8]. DN is a major cause of end-stage renal disease in many countries, and it is a life-threatening condition [9]. Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes, which is occasionally the initial manifestation of type 2 diabetic patients [10]. Regarding the microvascular complications of diabetes, the role of uric acid in the onset and progression of these complications was shown in some studies.

There is obscurity in this field, whether SUA is independently associated with the development of microvascular complications and mortality in T2DM. It is very much essential for secondary and tertiary prevention of microvascular complications. So, the aim of this study was to evaluate the association between serum uric acid levels in diabetic patients with and without microvascular complications.

Materials and methods

A cross-sectional study was conducted on patients with known diabetes or newly detected diabetes or impaired glucose tolerance treated on OPD basis or in patients in NRI Medical College in the department of General Medicine. The study was conducted from January 2018 to June 2018. A total of 80 subjects were included in the study and divided into two groups, 40 with microvascular complications of diabetes and 40 without microvascular complications.

Inclusion criteria

- Diabetics with microvascular complications of diabetes.
- Diabetics without microvascular complications of diabetes.

Age above 18 years Diabetics were diagnosed according to American Diabetes Association Recommendations. Microvascular complications

of diabetes include retinopathy, nephropathy, and neuropathy which are long-term complications of diabetes affecting small blood vessels.

Exclusion criteria

- Patients having diagnosed with gout.
- Patients having malignancies.
- Diagnosed conditions where uric acid levels are elevated.

Method of collecting data

After signing a written informed consent for each patient, the subjects completed a questionnaire including general information, smoking status, duration of diabetes, Family history of diabetes, type of medication and history of foot ulcer. Then, the height, weight and blood pressure were recorded. A thorough general physical examination including anthropometric measurement in the form of height, weight, BMI and systemic examination was done. Biochemical investigation with standard laboratory technique in the form of CBC, fasting and post-prandial blood glucose estimation, urine examination, glycosylated hemoglobin estimation (HPLC method), lipid profile, blood urea, uric acid, and serum creatinine estimation were done.

Method of uric acid estimation

The uric acid level was measured by uricase – pap methodology. Uric acid is degraded by uricase to allantoin and H_2O_2. The product H2O2 is then quantitated by the use of catalase and aldehyde dehydrogenase. The increase in NADPH concentration, measured by the change in absorption at 339 nm or 334 nm is proportional to the amount of uric acid.

Ophthalmologic examination for evidence of diabetic retinopathy was done. For the diagnosis of peripheral diabetic neuropathy, a nerve conduction study was done. Ankle reflex, vibration test, sensations were recorded. Nephropathy by blood urea nitrogen, serum creatinine, urine examination was done. eGFR was calculated for all patients by the MDRD formula. Ultrasound abdomen was done for selected patients for kidney size and echotexture.

A p-value of 0.05 was considered statistically significant and IBM 22 software was used for statistical analysis [11].

Results

The total number of subjects included in this study was 80. The age of the subjects with Type 2 DM without complications ranged from 29 to 96 years. The age of the subjects with Type 2 DM with complications ranged from 36 to 85. The mean age was 54.88 ±12.77, 60.33 ±12.33 respectively. Diabetic subjects with microvascular complications had higher Serum uric acid levels (5.56±2.39) and lower GFR (59.90 ±34.71) and it was statistically significant (**Table – 1**).

The duration of diabetes was higher among those who had complications. There was a significant difference with respect to the duration of diabetes among the patients who had complications and without complications. Most patients presented without symptoms of diabetes (**Table – 2**).

Most of the cases had 80% Retinopathy, followed by 27.5% Neuropathy, 20% had Nephropathy (**Table – 3**).

Mean HbA1c was highest among diabetics with complications like neuropathy, retinopathy than nephropathy. This difference was not statistically significant. Serum creatinines, blood urea, BUN were high among Diabetic patients with Nephropathy and the difference was statistically significant. Mean Uric acid was highest among Diabetic with complications. Nephropathy patients had lower uric acid than in retinopathy and neuropathy (**Table – 4**).

Hyperuricemia (28.57%) was seen among patients with more than 10 years duration of diabetes (**Table - 5**).

Table - 1: Demographic and clinical parameters between with and without microvascular people in Type2 DM (N=80).

Parameter	**Type 2 DM without microvascular complications (N=40)**	**Type 2 DM with microvascular complications (N=40)**	**P value**
Age (range)	29-96	36-85	*
Mean Age	54.88 ± 12.77	60.33 ±12.33	0.0704
Age group			
<=40	5 (12.5%)	3 (7.5%)	0.037
41-60	26 (65%)	17 (42.5%)	
>60	9 (22.5%)	20(50%)	
Gender			
Male	18 (45%)	20 (50%)	0.65
Female	22 (55%)	20 (50%)	
BMS	26.78 ±5.57	28.41 ±6.11	0.213
FBS	212.40 ±87.44	198.58 ±99.33	0.5109
PPBS	306.03 ±85.46	298.68±102.35	0.728
RBS	269.08±143.29	247.23±144.98	0.4998
HbA1C	10.60 ±2.77	14.30 ±19.58	0.24
Serum uric acid	3.86 ±1.28	5.56±2.39	<0.001
eGFR	95.66 ±29.04	59.90 ±34.71	<0.001

*No statistical test was applied- due to 0 subjects in the cells.

Table - 2: Comparison of Duration of diabetes (months), symptoms &lipid profile in diabetic patients between with & without Complications (N=80).

Parameter	**DM without Complications (N=40)**	**DM with Complications (N=40)**	**P-value**
Duration of diabetes in Months	40.05±52.68	84.57±84.57	0.006
Overall Symptoms			
Nil	39(97.5%)	28(70%)	*****
Yes	1(2.5%)	12(30%)	
Individual symptoms			
Blurring	0(0%)	3(7.5%)	
Dec urine	0(0%)	2(5%)	
Numbness	0(0%)	4(10%)	
Pain paras	0(0%)	1(2.5%)	
Polydipsia	1(2.5%)	2(5%)	
Family History			
Present	10(25%)	10(25%)	**1.00**
Absent	30(75%)	30(75%)	
Total cholesterol(mg/dl)	161.80±32.71	159.45±51.85	0.81
TGL (mg/dl)	228.80±125.91	209.45±125.58	0.49
HDL (mg/dl)	32.95±8.08	30.35±9.68	0.19
LDL (mg/dl)	73.30±37.66	79.40±41.37	0.49

*No statistical test was applied- due to 0 subjects in the cells.

Table - 3: Complications in type2 DM with microvascular complications people (N=40).

Complications	Frequency (%)
Nephropathy	8 (20)
Retinopathy	32 (80)
Neuropathy	11 (27.5)
Nephropathy + Retinopathy	7 (17.5)
Retinopathy + Neuropathy	2 (5)
Neuropathy + Nephropathy	3 (7.5)

Table - 4: Comparison of HbA1c and Various renal parameters among different groups (N=80).

Parameter	DM without compilations (N=40)	DM with complications other than nephropathy (N=32)	DM with nephropathy (N=8)	P-value
HbA1 C	10.59±2.77	17.25 ±26.14	10.68±3.08	0.23
eGFR	102.35±33.9	93.77±22.79	28.94±15.44	<0.001
Serum creatinine	0.78±0.21	0.83±0.21	3.06±2.55	<0.001
Blood Urea	28.7±12.2	30.50±10.6	98.78±74.15	<0.001
BUN	10.19±4.37	10.0±2.87	40.67±30.51	<0.001
Uric acid	3.85±1.27	6.61±1.81	6.3±2.66	<0.001

Table - 5: Association between Uric acid and Duration of Diabetes Mellitus (N=80).

Uric acid	Duration of DM			Total
	<5 years	5 to 10 years	>10 years	
<3 (Hypouricemia)	12 (23.07%)	3 (21.42%)	2 (14.28%)	17
3 to 7 (Normal)	37 (71.15%)	10 (71.42%)	8 (57.14%)	55
> 7(Hyperuricemia)	3 (5.76%)	1 (7.14%)	4 (28.57%)	8
Total	52	14	14	80

P-value = 0.158

Discussion

Uric acid is a metabolic end product of purine metabolism has been implicated in various diseases. Of late this molecule has gained momentum and is a widely debated molecule as a cause or consequence with respect to the complications of diabetes. So the present study was conducted to find the association of this molecule with diabetes and microvascular complications particularly, nephropathy, retinopathy, and neuropathy.

In the current study majority of the diabetic subjects without microvascular complications (65%) belonged to 41 to 60 years of age group and diabetic subjects with microvascular complications (50%) belonged to more than 60 years of age group and the difference was statistically significant. Diabetic subjects with microvascular complications had higher Serum uric acid levels (5.56±2.39) and lower GFR (59.90 ±34.71) and it was statistically significant. Similar results were reported by Rosolowsky ET, et al. [12] in which Serum uric acid levels were 5.2 and GFR was 98.7 among diabetic patients. The reason may be that serum hyperuricemia results in reduced renal clearance of uric acid may involve a reduced GFR or dysfunctional handling of filtered uric acid by proximal tubules.

The main finding of the present study was that plasma uric acid was highest among Diabetic with complications (6.61±1.81). Nephropathy patients had lower uric acid (6.3±2.66) than in subjects with retinopathy and neuropathy. The

lowest plasma uric acid levels were found in diabetic patients without microvascular complications (3.85±1.27). In a meta-analysis done by Xu Y, et al. [13] on 9 relevant studies involving a total of more than 20,981 sample size they suggested a significantly positive correlation with each 0.1 mmol/l increase in SUA leads to a 28% increase for the risk of vascular complications in T2DM and a 9% increase for the risk of mortality. The results were in accordance with M. Modan M, et al. [14] study who reported that elevated serum uric acid is a feature of hyperinsulinemia and insulin resistance. Serum uric acid showed a positive association with plasma insulin response (sum of 1- and 2-hour post glucose load levels) in both males ($r=0.316$, $p< 0.001$). Nakanishi N, et al. [15] in their study, found that Serum Uric Acid level is closely associated with an increased risk for hypertension and IFG or Type II diabetes.

In the current study, majority of the subjects had (80%) retinopathy, followed by 27.5% had neuropathy and 20% had nephropathy. Increased serum uric acid levels were observed in patients with retinopathy and neuropathy. Comparing retinopathy, similar results were observed in a cross-sectional study done by Yanko L, et al. [16], in which SUA increase was positively related to the progression of retinopathy. Whereas in a prospective study done by Feldman T, et al. [17] who followed 95 consecutive diabetes clinic patients for 15 years, had indicated that higher SUA levels were not related to diabetic retinopathy. Comparing neuropathy, Papanas N, et al. [18] evaluated the serum uric acid levels in type 2 diabetic patients with and without peripheral neuropathy and found that serum uric acid increased in 64 patients with neuropathy versus 66 matched patients without neuropathy according to NSS-NDS criteria.

In the current study, 20% had nephropathy had lower uric acid than in retinopathy and neuropathy. However, Hovind P, et al. [19] studied 277 patients with type 1 diabetics that showed uric acid level soon after the onset of type 1 diabetes was independently associated with the risk for later development of diabetic nephropathy. Similarly, Chuengsamarn S, et al. [20], in their study found that prevalence of chronic vascular complications in T2DM patients, diabetic nephropathy, diabetic retinopathy, and diabetic peripheral neuropathy was significantly correlated with the increase of uric acid level, 9.99 (4.4–22.8), 4.43 (1.3–15.1), 4.37 (1.5–12.9) respectively. Kodama S, et al. [6] in their study also suggested that an increase of uric acid and microalbuminuria levels may be novel surrogate markers to predict the incidence of DM.

Serum uric acid can function as a proinflammatory molecule with the capacity to act as both a pro-oxidant and an antioxidant [21]. Hyperinsulinemia resulting from insulin resistance in T2DM negatively affects renal excretion, increases rates of renal reabsorption, and the production of uric acid. Uric acid has been shown to play roles in the induction of some inflammatory cytokines (hs-CRP, IL-6, and TNF-α), and oxidative stress. The induction of the cytokines and oxidative stress was speculated to contribute to the pathogenesis of diabetic vascular complications [22].

The present study reported hyperuricemia (28.57%) among patients with more than 10 years duration of diabetes. The results are contrary to the study conducted by Meena R, et al. [23] who observed lower levels of serum uric acid was seen in patients with longer duration of diabetes, 2.58±0.56 (>8 years) when compared with shorter duration of diabetes, 3.59±0.98 (0-5 years). The possible reason may be due to increased excretion of uric acid over the years.

Conclusion

The increase of uric acid levels was significantly associated with the severity of chronic vascular complications in T2DM patients. Uric acid is useful as predictors for monitoring the chronic micro/macro-vascular complications in patients with type 2 diabetes. Regular measurements of uric acid levels in patients with type 2 diabetes

could help physicians in clinical practice to be alerted to the development of chronic microvascular complications.

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